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Lectin receptors expressed on myeloid cells

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Summary (250 words)

Lectins recognise a diverse array of carbohydrate structures and perform numerous essential biological functions. Here we focus on only two families of lectins, the Siglecs and C-type lectins. Triggering of intracellular signalling cascades following ligand recognition by these receptors can have profound effects on the induction and modulation of immunity. In this chapter, we provide a brief overview of each family and then focus on selected examples which highlight how these lectins can influence myeloid cell functioning in health and disease. Receptors that are discussed include Sn (siglec-1), CD33 (siglec-3) and Siglecs-5, -7, -8, -9, -10, -11, -14, -15, -E, -F, and -G as well as Dectin-1, MICL, Dectin-2, Mincle/MCL and the macrophage mannose receptor.

Introduction

Lectins, defined as proteins which recognise carbohydrates, perform numerous essential biological functions. Recognising a diverse array of carbohydrate structures, vertebrate lectins have been subdivided into several structurally distinct families which can be located intracellularly (such as the intracellular M-type family of lectins which function primarily in the glycoprotein secretory pathway), in the plasma membrane (such as some members of the C-type lectin and Siglec families, which are involved in pathogen recognition and immune regulation) or are secreted into the extracellular milieu (such as some members of the galectin family, which serve several homeostatic and immune functions) (Table 1). Given the particular focus of this book, we will restrict our discussion in this chapter to selected myeloid- and plasma-membrane expressed members of only two families, the C-type lectins and siglecs. We will provide a brief overview of each family and then focus on selected

illustrative and detailed examples which highlight how these lectins influence myeloid cell functioning in health and disease. For an overview on the other lectin families, the reader is referred to an excellent website (<http://www.imperial.ac.uk/research/animalletins/ctld/lectins.html>).

Siglecs

Siglecs are a distinct subgroup of the immunoglobulin (Ig) superfamily that have evolved to use sialylated glycans as their predominant ligands (1). Siglecs have been mainly defined in mammalian species, but clear orthologues are also present in amphibia and fish (2). Siglec-like molecules have also been identified in streptococcal bacteria ((3)) and in an adenovirus capsid protein (4). In mammals, there are 2 subgroups of siglecs: (i) sialoadhesin (Sn, Siglec-1), CD22 (Siglec-2), MAG (Siglec-4) and Siglec-15 which are present in all species and (ii) CD33-related siglecs that vary considerably in composition between species and appear to be undergoing rapid evolution (Figure 1). Due to uncertainties in gene ontologies, the human CD33-related siglecs have been assigned numerical suffixes whereas the mouse CD33-related siglecs have been assigned alphabetical suffixes. All siglecs are type 1 membrane proteins containing a homologous N-terminal V-set Ig-like domain that recognises sialylated glycans, followed by variable numbers of C2 set domains. Recognition of sialic acid depends on a conserved structural template involving both hydrogen bonding networks, ionic and hydrophobic interactions, together with variable inter-strand loops that make contact with additional glycan residues and confer extended specificity to siglecs (5). A siglec-like Ig fold was recently seen in the regulatory myeloid receptors, PILR- α and - β , which mediate high affinity binding to mucin-like sialylated ligands via both protein- protein and protein-

sialic acid interactions (6, 7). Siglecs are expressed broadly across the haemopoietic and immune systems, except for MAG which is restricted to the myelin-forming cells of the nervous system, oligodendrocytes and Schwann cells (Figure 1). As discussed below, some siglecs are highly restricted to particular cell types, whereas others are more broadly expressed. In humans and mice, the major subgroup of cells lacking siglecs are CD4 and CD8 T cells, although in other species such as chimpanzees, Siglec-5 is reported to be expressed on all circulating T cells (8)

When expressed naturally at the cell surface, siglecs interact with sialic acid-containing ligands both *in cis* (on the same plasma membrane) and *in trans* (on the plasma membrane of different cells). The degree to which each occurs likely depends on the relative affinity, density and display of sialylated ligands as well as other poorly understood topographical constraints. Both types of interaction have been shown to play important roles in immune modulation (reviewed in (9, 10)). The cytoplasmic tails of most siglecs contain two or more tyrosine-based motifs that can be phosphorylated and recruit SH2-domain containing effector molecules. The most common motif is the immunoreceptor tyrosine-based inhibitory motif (ITIM) that has been identified in hundreds of receptors of the immune system (11).

Phosphorylated ITIMs exhibit high affinity for the tandem SH2-domain containing protein tyrosine phosphatases, SHP-1 and SHP-2, which are activated on binding to ITIMs and thereby potentially capable of modulating signalling functions of siglec-expressing cells (9). Many siglecs also possess ITIM-like motifs that appear to synergise with the ITIMs for efficient recruitment of SHP-1 and SHP-2 (12, 13). The same motifs are also important for the endocytic functions of many siglecs. Some siglecs possess a basic residue in the transmembrane region (Figure 1) that leads to

formation of a membrane complex with DAP-12, an adaptor with an immunoreceptor tyrosine based activation motif (ITAM). As a consequence, these siglecs have the potential to directly trigger signal transduction via Syk recruitment and activation. Links between glycan recognition by siglecs and subsequent intracellular signalling have been a major focus for many laboratories since their discovery, but the specific downstream targets and biochemical pathways remain elusive for the most part. The focus of this section will be siglecs that are expressed predominantly on human myeloid cells, namely Sn (siglec-1), CD33 (siglec-3) and Siglecs-5, -7, -8, -9, -10, -11, -14 and -15. Given the importance of mouse models in determining the biological functions of siglecs, the murine CD33-related Siglecs-E, -F, and -G will be grouped with their most closely-related human counterparts for comparative purposes.

Sialoadhesin (Siglec-1, CD169)

Sn is a prototypic siglec that was identified as a sialic acid-dependent erythrocyte receptor expressed by subsets of mouse resident tissue macrophages (14). Sn has an unusually large number of 17 Ig domains which appear conserved in mammals and reptiles (15). These are important for extending the sialic acid-binding site away from the plasma membrane to promote intercellular interactions. Sn prefers α 2-3-linked sialic acids over α 2-6- and α 2-8-linked sialic acids and does not bind sialic acids modified by hydroxylation (Neu5Gc) or 9-O-acetylation (e.g. Neu5,9Ac2) (16, 17).

In humans and mice, Sn expression appears specific for tissue macrophage subsets described as 'CD169+ macrophages' (18-20). These cells are abundant in

lymphoid tissues, notably subcapsular sinus macrophages in lymph nodes and marginal metallophilic macrophages in the spleens of rodents or perfollicular capillary sheaths in spleens of humans (21). These macrophage populations are strategically positioned to capture viruses and immune complexes from the afferent lymphatics and splenic sinuses respectively and may therefore share similar biological functions (22). Emerging evidence clearly shows that CD169⁺ macrophages play a key role in the capture of a broad range of viruses, including arteriviruses (23), retroviruses (24), herpes viruses (25, 26) and adenoviruses (27), and for the first two, this directly involves viral recognition by Sn. CD169⁺ macrophage capture of viruses is important for restraining viral spread to distal sites (28), but it can also promote viral transfer to neighbouring cells such as T cells (29, 30) and B cells (31) and directly prime CD8⁺ cytotoxic T cells for responses to viral antigens via cross-presentation (27). Interestingly, CD169⁺ macrophages in the spleen have been shown to act as “Trojan horses” for vesicular stomatitis viruses, permitting high viral replication that is important for stimulation of protective adaptive immune responses (32). In addition to viruses, CD169⁺ macrophages can capture apoptotic tumour cells and cross-present tumour antigens to drive anti-tumour cytotoxic CD8 T cell responses (33). Conversely, uptake of apoptotic cells by CD169⁺ macrophages can drive tolerance of self-reactive T cells via induction of the chemokine CCL22 (34). CD169⁺ macrophages can also transfer exogenous antigens to DCs and promote cross presentation to CD8 T cells (35) and transfer antigens to B cells (36) and NKT cells (37) to promote cellular activation. Besides its constitutive high expression on tissue macrophage subsets, Sn can also be induced strongly on monocytes, macrophages and monocyte-derived DCs *in vitro* by type I interferons or agents such as viruses and TLR ligands that induce interferon

production (24). Accordingly, Sn is upregulated on circulating monocytes in HIV-infected individuals and on macrophages in rheumatoid arthritis (38), primary biliary cirrhosis (39), systemic sclerosis (40) and systemic lupus erythematosus (SLE) (41). Sn expression on inflammatory macrophages has been associated with favourable prognosis in colorectal cancer (42) and in endometrial carcinoma (43), but with a more severe disease in proliferative glomerulonephritis (44). Many of the above disease associations may reflect exposure of macrophages to interferons rather than being causally related. Indeed, in the BWF1 murine model of spontaneous SLE, there was no influence of Sn-deficiency on disease severity (45). However, in mouse models of inherited neuropathy (46-48), autoimmune uveoretinitis (49) and experimental allergic encephalomyelitis (EAE) (50), Sn-deficient mice exhibited reduced inflammation accompanied by reduced levels of T cell and macrophage activation. In the EAE model, this appears to be due to a Sn-dependent suppression of CD4⁺ FoxP3⁺ regulatory T cell expansion thereby promoting inflammation (50) whereas in the other CNS models, Sn-dependent regulation of CD8 T cells is important (46). The upregulation of sialylated ligands for Sn on activated T cell populations is likely to be an important determinant in mediating the Sn-dependent suppression of T cell subsets and function (51). Sn can also efficiently mediate the capture and uptake of exosomes released from B lymphocytes following apoptosis and therefore play a role in antigen presentation to T cells (52, 53) .

A role for Sn in phagocytic interactions of macrophages with various sialylated bacterial and protozoal pathogens was initially demonstrated, including *Neisseria meningitidis* (54), *Campylobacter jejuni* (55) and *Trypanosoma cruzi* (56). Sn-dependent targeting of heat-killed *C. jejuni* to splenic red pulp macrophages led to a rapid induction of type I interferon and pro-inflammatory cytokines, in a MyD88-

dependent manner, suggesting a host protective role for Sn against sialylated bacteria (57). This was also supported in an infection model using a sialylated strain of Group B streptococcus (GBS), where Sn-deficient mice exhibited reduced bacterial spread (58). However, this protective role for Sn was only seen in neutrophil-depleted mice, suggesting that Sn-dependent macrophage bacterial uptake can provide a backup defence in the event of neutrophils failing to clear the bacteria. Conversely, Sn expression on macrophages and monocyte-derived DCs can be exploited by enveloped viruses displaying host-derived sialic acids, leading to their capture, uptake and dissemination. This was first seen with the porcine reproductive and respiratory syndrome virus which targets lung alveolar macrophages of pigs (23) and more recently with HIV (24) and other retroviruses (31, 59). On HIV, Sn can recognise both gp120, a sialylated glycoprotein and GM3, a monosialylated ganglioside terminating in NeuAc α 2-3Gal (30, 60-62). GM3 is packaged into the HIV envelope during the budding from infected cells which occurs in lipid rafts (63). On monocyte-derived DCs, Sn interactions with HIV lead to membrane invaginations containing viral particles that are very efficiently transferred to T cells in a process known as 'trans-infection' (30). *In vivo* evidence that Sn promotes retroviral trans-infection was obtained following infection of mice using murine leukaemia virus where trans-infection of B cells depended on the expression of Sn on lymph node sinus-lining macrophages (31).

Although Sn is unusual amongst siglecs in not having well-defined signalling motifs in its cytoplasmic tail, recent reports have suggested it can associate with the ITAM adaptor, DAP12 and either suppress type 1 interferon production or stimulate TGF- β production (64, 65). These studies were both done using RNA knockdown

approaches to suppress Sn expression and the physiological significance of the findings should be confirmed using primary macrophages from Sn-deficient mice.

CD33 (Siglec-3)

CD33 is a marker of early human myeloid progenitors and leukemic cells, and is also expressed on monocytes, tissue macrophages, NK cell subsets and weakly on neutrophils. It has 2 Ig domains and was the first of the CD33-related siglecs to be characterized as an inhibitory receptor, suppressing activation of FcγRI and recruiting SHP-1 and SHP-2 (66). CD33 has some preference for α2-6- over α2-3-sialylated glycans and binds strongly to sialylated ligands on myeloid leukaemic cell lines (67). The restricted expression of CD33 has been exploited in the treatment of acute myeloid leukemia using Gemtuzumab, a humanized anti-CD33 monoclonal antibody coupled to the toxic antibiotic calicheamicin. Binding of anti-CD33 mAbs to CD33 triggers endocytosis of the bound antibody. This depends on ITIM phosphorylation, recruitment of the E3 ligase Cbl, and ubiquitylation of the CD33 cytoplasmic tail (68-70). Selective expression of CD33 on leukaemic progenitor cells also makes it an attractive target for therapy using chimeric antigen receptors expressed on cytotoxic T cells.

Recently, two co-inherited single-nucleotide polymorphism (SNPs) have been associated with protection of humans against late-onset Alzheimer's disease in genome-wide association studies. These SNPs result in increased exon 2 skipping, leading to raised levels of CD33 lacking the V-set domain and reduced levels of full-length CD33 (71). Since full-length CD33 can inhibit microglial cell uptake of Aβ protein in a sialic acid dependent manner (72, 73), it is thought that individuals

lacking the protective SNPs may accumulate more toxic A β proteins, thus driving pathology. Targeting CD33 using antibodies that either inhibit function or promote internalisation and degradation may be a useful approach to treating Alzheimer's disease.

The murine orthologue of CD33 exists as two spliced forms that differ in the cytoplasmic tail, neither containing the typical ITIM found in most other CD33-related Siglecs (74). Furthermore, mCD33 has a lysine residue in the transmembrane sequence and may therefore couple to the DAP-12 transmembrane adaptor, as shown for mouse Siglec-H (75) and human Siglecs-14 (76), -15 (77) and -16 (78). In contrast to hCD33, mCD33 in the blood is expressed mainly on neutrophils rather than monocytes, which also suggests a nonconserved function of this receptor (79).

Siglec-5 (CD170) and Siglec-14

The SIGLEC-5 and SIGLEC-14 genes are adjacent to each other on chromosome 19 and encode proteins containing four and three Ig-like domains respectively. The first two Ig domains of Siglecs-5 and -14 share more than 99% sequence identity but then diverge. Siglec-5 is an inhibitory receptor with typical ITIMs, whereas Siglec-14 is complexed with DAP12 and mediates activatory signalling. Both Siglecs-5 and -14 bind similar ligands, with a preference for the sialylTn structure (Neu5Ac α 2-6GalNAc α) (76). Although many antibodies to Siglec-5 cross-react with Siglec-14, specific antibodies have shown that while Siglec-5 is expressed on neutrophils and B cells, Siglec-14 is found at low levels on neutrophils and monocytes. A SIGLEC-14 null allele is frequently present in Asian populations but is less common in Europeans (80). This is due to a recombination event between the 5' region of the

SIGLEC-14 gene and the 3' region of the SIGLEC-5 gene, resulting in a fusion protein that is identical to Siglec-5, but expressed in a Siglec-14-like manner. Individuals with chronic obstructive pulmonary disease (COPD) who are SIGLEC-14 null, exhibited reduced exacerbation attacks compared with individuals expressing Siglec-14 (80). Siglec-5 can bind sialylated strains of *N. meningitidis* and both Siglecs-5 and -14 can bind sialylated strains of *Haemophilus influenzae* implicated in COPD exacerbations and trigger inhibitory and activatory responses respectively (80). Thus, the absence of Siglec-14 on neutrophils would lead to reduced inflammatory responses in SIGLEC-14 null individuals. Besides expression on leukocytes, both Siglecs-5 and -14 are found on human amniotic epithelium and may influence responses to GBS infection and the frequency of preterm births in infected mothers (81). Besides mediating sialic acid-dependent interactions with host cells and pathogens, Siglecs-5 and -14 can mediate sugar-independent interactions with some strains of GBS via recognition of the beta protein (81). A recent study also demonstrated that the non-glycosylated danger associated molecular pattern (DAMP) protein HSP70, can bind to Siglecs-5 and -14 and modulate cellular responses (82). There are no obvious equivalents of Siglecs-5 or -14 in mice making it difficult to study this interesting pair of receptors in animal models.

Siglecs-7, -9, -E

Siglecs-7 and -9 share a high degree of sequence similarity, and appear to have evolved by gene duplication from an ancestral gene encoding a 3-Ig-domain inhibitory siglec, represented in mice by Siglec-E. Siglec-7 is the major Siglec on human NK cells and is also seen at lower levels on monocytes, macrophages, DCs

and a minor subsets of CD8 T cells (83-85). Siglec-7 has also been detected in platelets, basophils and mast cells where it may modulate survival and activation (85). Siglec-9 is prominently expressed on neutrophils, monocytes, macrophages and DCs, ~30% of NK cells and minor subsets of CD4 and CD8 T cells (86, 87). Despite high sequence similarity, Siglec-7 binds strongly to α 2-8-linked sialic acids present in 'b-series' gangliosides (and some glycoproteins, whereas Siglec-9 prefers α 2-3-linked sialic acids (88). Sulfation of the SLe^x structure can strongly influence recognition by both Siglecs, with Siglec-9 preferring, 6-sulfo-SLe^x, and Siglec-7 binding well to both 6-sulfo-SLe^x and 6'-sulfo-SLe^x (89). It has recently been shown that Siglec-9 can bind strongly to high molecular weight hyaluronan, and that its ligation on neutrophils leads to suppression of cellular activation (90).

Siglec-E in mice exhibits a combination of some features of Siglec-7 and Siglec-9, being mainly expressed on neutrophils, monocytes and macrophages, with sialic acid binding preferences that span those of both Siglecs-7 and -9 (91). Similar to T cells, NK cells in mice appear to lack expression of inhibitory Siglecs. Siglec-E is an important inhibitory receptor of neutrophils, as initially demonstrated in a LPS-induced lung inflammation model in which Siglec-E-deficient mice exhibited exaggerated CD11b-dependent neutrophil influx (92). This was found to be linked to Siglec-E-dependent production of reactive oxygen species by neutrophils triggered on the CD11b ligand fibrinogen which suppressed neutrophil recruitment to the lung (93). Siglec-E dependent inhibition of neutrophil function has also been proposed to be a mechanism underlying an exaggerated ageing phenotype observed in one strain of Siglec-E-deficient mice (94). Several studies have also demonstrated inhibitory functions of Siglec-E on macrophages and dendritic cells, including suppression of proinflammatory cytokine production in response to TLR ligands and

promotion of regulatory T cells in response to sialylated antigens (95-99).

Furthermore, targeting Siglec-E on macrophages with sialylated nanoparticles was shown to block inflammatory responses *in vitro* and *in vivo* (100).

Tumour cells often upregulate cell surface sialylated glycans and it appears that these may be important in Siglec-dependent dampening of anti-tumour immunity. Siglecs-7 and -9 can both suppress NK cell cytotoxicity against tumour cells expressing relevant glycan ligands (101-103). Siglec-9 and Siglec-E can also dampen neutrophil activation and tumour cell killing, while ligation of Siglec-9 or Siglec-E on macrophages by tumour glycans seems to suppress formation of tumour promoting M2 macrophages (98). Studies with GBS have also demonstrated that sialylated bacteria can subvert innate immune responses by targeting Siglec-9 and Siglec-E on neutrophils and macrophages, resulting in attenuation of phagocytosis, killing and proinflammatory cytokine production (104, 105).

Siglec-8, F

Siglec-8 has 3 Ig domains and is expressed on eosinophils and mast cells, with weaker expression on basophils (106, 107). It binds strongly to 6'-sulfo-SLex and to mucins isolated from bronchial tissues (108, 109), but endogenous mucin ligands do not seem to require sulfation for strong binding (110). In mast cells, antibodies to Siglec-8 can inhibit FcεR1 triggered degranulation responses in line with its role as an inhibitory receptor (111). In eosinophils, much attention has focussed on the role of Siglec-8 in triggering apoptosis, which can occur following cross-linking with anti-

Siglec-8 antibodies or sialoglycan polymers (112, 113). Apoptosis depends on generation of reactive oxygen species and caspase activation and is paradoxically enhanced in the presence of cytokine “survival” factors such as GM-CSF and interleukin-5 (113). A role for Siglec-8 in the pathogenesis of asthma has been suggested by upregulation of Siglec-8 ligands in inflamed lung tissue (109) and by associations of Siglec-8 polymorphisms with asthma (114).

Although there is no ortholog of Siglec-8 in mice, the four-Ig domain mouse Siglec-F is expressed in a similar way to Siglec-8 on eosinophils, has a similar glycan-binding preference for to 6'-sulfo-SLex and appears to have acquired similar functions through convergent evolution (115-117). There are some important differences, however. Siglec-F can recognise a broader range of α 2-3-linked sialic acids, it is also expressed on alveolar macrophages and triggers weaker apoptosis using different signalling pathways (118). Siglec-F-null mice show exaggerated eosinophilic responses in certain lung allergy models, suggesting that Siglec-F negatively regulates eosinophil production and/or survival following immunological challenge (119, 120). Interestingly, Siglec-F ligands in the airways and lung parenchyma were also up-regulated during allergic inflammation, but these did not appear to require sulfation to mediate strong binding to Siglec-F (110).

Siglec-10, G

Siglec-10 has five Ig-like domains and in addition to the ITIM and ITIM-like motifs, displays an additional tyrosine-based motif in its cytoplasmic tail (121-123). It is expressed at relatively low levels on several cells of the immune system, including B cells, monocytes and eosinophils (122). It can also be strongly upregulated on

tumour-infiltrating NK cells in hepatocellular carcinoma where its expression was negatively associated with patient survival (124). It is the only CD33-related human Siglec that has a clear-cut orthologue in mice, designated Siglec-G (9). Both Siglec-10 and Siglec-G prefer Neu5Gc over Neu5Ac in both α 2-3 and α 2-6 linkages (125). Similar to Siglec-10 in humans and pigs (126), Siglec-G is mainly expressed on B cells and subsets of dendritic cells and weakly on eosinophils (127, 128). Mice deficient in Siglec-G show a tenfold increase in numbers of a specialized subset of B lymphocytes, the B1a cells, which make natural antibodies (129). These Siglec-G deficient B1a cells also show exaggerated Ca-fluxing following BCR cross-linking. Studies using 'knockin' mice carrying an inactivating mutation in the sialic acid binding site of Siglec-G show a similar phenotype (127). This appears to be due to a requirement of sialic acid-dependent cis-interactions between Siglec-G and the BCR. On DCs, Siglec-G has been proposed to regulate cytokine responses to DAMPs released by necrotic cells in sterile inflammation. This is thought to be due to a dampening effect of cis-interactions between Siglec-G and the heavily sialylated DAMP receptor, CD24 (130). Disruption of this interaction through sialidases released by bacteria such as *Streptococcus pneumoniae* may be important in triggering inflammatory responses in sepsis (131). A recent study has also shown that pseudaminic acid expressed on the flagella of *C. jejuni* can be recognised by Siglec-10 and trigger IL-10 production in dendritic cells (132). This suggests a novel form of glycan recognition by Siglec-10 that is exploited by some pathogens.

Siglecs-11 and -16

Siglecs-11 and 16 are paired inhibitory and activatory receptors, with 5 and 4 Ig domains respectively (78, 133). In most humans, the SIGLEC-16 gene has a 4 base pair deletion and only ~35% of humans express one or two functional alleles. The extracellular regions of these proteins are >99% identical due to gene conversion events, and anti-Siglec-11 mAb 4C4 cross-reacts with Siglec-16. Siglec-11 binds weakly to α 2-8-linked sialic acids in vitro. Siglec-11 appears to be absent from circulating leukocytes, but is expressed widely on populations of tissue macrophages, including resident microglia in the brain, where high levels of α 2-8-linked sialic acids are present on gangliosides. Expression of Siglec-11 on microglia can impair their phagocytosis of apoptotic cells and neurotoxicity (134). Polysialic acid presented by neural cell adhesion molecule, NCAM, is also α 2-8-linked and was shown to be recognised by Siglec-11 on macrophages and suppress LPS-dependent TNF- α production and phagocytosis triggered by LPS exposure (134, 135). Interestingly, microglial expression appears to be unique to humans (136). In mice, its function may be mediated by Siglec-E which is similarly expressed on microglia and able to mediate neuroprotective effects in response to inflammatory signals (96). The activating receptor Siglec-16 is also present on macrophages, including those in the brain, but functional studies have not been reported (78).

Siglec-15

Siglec-15 was first described in 2007 as a highly conserved and ancient Siglec found in vertebrates (77). It lacks the typical arrangement of cysteines seen in the V-set Ig domain of other siglecs and has an unusual intron-exon arrangement. Nevertheless it can bind the SialylTn structure (Neu5Ac α 2-6GalNAc α), with weaker binding to 3'

sialyllactose. It is associated with DAP12 and also has a tyrosine-based motif in the cytoplasmic tail. On macrophages, interactions with SialylTn antigens expressed by tumour cells was shown to trigger TGF β production which could be important in immunosuppression and promoting tumour growth (137).

Although first reported as being expressed on macrophages and dendritic cells in human lymphoid tissues, subsequent work has established that Siglec-15 is most strongly expressed in osteoclasts and their precursors where it plays an important role together with RANK ligand in triggering osteoclast differentiation (138-141). Osteoclasts are key cells involved in bone degradation and share a common hemopoietic progenitor with macrophages. Mice lacking Siglec-15 show a mild osteopetrosis and impaired osteoclast differentiation (140, 141). Specific antibodies directed to Siglec-15 are able to phenocopy this due to antibody-induced internalisation and degradation of Siglec-15 (142). Siglec-15 therefore provides a novel target for diseases involving excessive osteoclast activation and bone loss, such as menopause-related osteoporosis.

C-type lectin receptors

C-type lectin receptors (CLR) are a diverse collection of over 1000 proteins and are the largest lectin family (143). All of these receptors possess at least one C-type lectin-like domain (CTLD), a characteristic fold formed by disulphide linkages between highly conserved cysteine residues (143). Based on their phylogeny and structure, CLRs have been divided into 17 groups which are either membrane bound or secreted (143). The term C-type lectin originated from initial observations that these receptors required Ca²⁺ for carbohydrate recognition. However, we now know

that not all CLRs require Ca^{2+} for ligand recognition and that these receptors can recognize a much more diverse range of ligands, such as lipids and proteins for example. Many of these receptors have also been shown to bind to different classes of ligands (ie: they are multivalent), and can recognise both endogenous and exogenous ligands.

A great many CLRs have essential roles in immunity. A key example are the endothelial-expressed selectins which function as adhesion molecules by binding cell surface glycoproteins on leukocytes and play a critical part in leucocyte migration during inflammation (144). Other examples include the secreted collectins, such as the surfactant proteins, which function in both pulmonary physiology and immunity, and serum mannose-binding protein (MBL), which has an essential role in triggering complement activation through MBL-associated serine proteases in response to microbial infection (145). The focus of the rest of this section, however, will be on selected transmembrane receptors that are widely expressed by myeloid cells and have been extensively characterized in murine models, including Dectin-1, MICL, Dectin-2, Mincle/MCL, and the macrophage mannose receptor. Detailed descriptions of these molecules will serve as illustrative examples of varied nature of C-type lectins and their importance in myeloid cell function in health and disease. The functions and properties of other myeloid expressed CLRs, including well characterised receptors such as DC-SIGN, can be found in several excellent reviews (146-148).

Dectin-1 (CLEC-7A)

Dectin-1 is one of the best characterised myeloid expressed CLR, and this type II transmembrane receptor belongs to group V within the CLR family. Dectin-1 contains

a single extracellular C-type lectin-like domain (CTLD), a stalk region, a single-pass transmembrane domain and a cytoplasmic tail containing signalling motifs, including an Immuno-receptor Tyrosine based Activation-like Motif (ITAM-like or hem-ITAM) and a tri-acidic motif (Figure 2). Dectin-1 is alternatively spliced into two major isoforms, differing by the presence or absence of the stalk region, which are expressed differentially in different cell types and mouse strains and which have slightly different functionalities (149). The receptor is *N*-glycosylated, which can affect its expression and function (150), and is predominantly expressed by myeloid cells, including monocytes, macrophages, dendritic cells and neutrophils (151). There is also evidence for expression of this receptor on B-cells and subsets of T-cells, and it may be unregulated on epithelial cells during inflammation (151-154).

Through mechanisms which are not yet completely understood, the CTLD of Dectin-1 is able to recognise β -1,3-glucan containing carbohydrates (155). These carbohydrates are found predominantly in fungal cell walls, and consequently there has been considerable focus on the role of Dectin-1 in anti-fungal immunity. Indeed, Dectin-1 recognises many fungal species, including major human pathogens such as *Aspergillus*, *Candida*, *Coccidioides* and *Pneumocystis* (156). There is now substantial evidence that Dectin-1 plays an essential role in anti-fungal immunity: several polymorphisms of this receptor in humans (including a Y238X polymorphism which essentially renders homozygous individuals Dectin-1 deficient) have been linked to increased susceptibility to mucocutaneous fungal infections or fungal induced inflammation in the gut (157-159). Moreover, Dectin-1 knockout mice are more susceptible to systemic and mucocutaneous infections with several pathogens (160-162). However, the requirement for Dectin-1 for controlling *C. albicans in vivo* is

dependent upon the fungal strain, which undergo differential changes in their cell wall during infection (163).

In addition to fungi, Dectin-1 can recognise mycobacteria. How Dectin-1 recognises these pathogens is unknown and although shown to promote IL-12 responses *in vitro*, the receptor does not appear to play an essential role in anti-mycobacterial immunity *in vivo* (164, 165). Dectin-1 has also been implicated in the recognition of other pathogens, including *Leishmania* (166).

Dectin-1 was originally identified as acting as a T-cell costimulatory molecule through recognition of an endogenous ligand (167), but the nature of this ligand remains elusive. Several other endogenous ligands have been described, including vimentin, through which Dectin-1 was thought to be involved driving lipid oxidation in atherosclerosis (168). However, Dectin-1 deficiency was subsequently found not to affect atherosclerosis development in mouse models (169). Dectin-1 has also been implicated in the reverse transcytosis of sIgA-antigen complexes by intestinal M cells and induction of subsequent mucosal and systemic antibody responses (170). Moreover, in the presence of galactosylated IgG1, Dectin-1 associates with FcγRIIB resulting in the inhibition of complement-mediated inflammation (171). In response to intestinal mucus, FcγRIIB, along with another lectin, galectin-3, complex with Dectin-1 to promote the anti-inflammatory properties of DCs, enhancing homeostasis and oral tolerance (172). Most recently, a protective role for Dectin-1 in antitumor immunity has been demonstrated. Mechanistically, Dectin-1 mediated recognition of N-glycan structures on tumour cells was shown to augment NK-mediated killing and, in a model of hepatocarcinogenesis, act protectively by suppressing TLR4 signalling (173, 174).

Upon recognition of β -glucans, Dectin-1 can activate Syk-dependent and Syk-independent intracellular signalling cascades. Surprisingly, the activation of Syk was shown to require the tyrosine phosphatase SHP-2, which acted as a scaffold and facilitated the recruitment to Syk to Dectin-1 (175). The ability of Dectin-1 to induce Syk-dependent signalling pathways is mediated by a single phosphorylated tyrosine residue in the ITAM-like motif within the cytoplasmic tail and is likely to require receptor dimerization (176). Signalling through this pathway involves PKC δ and the CARD9-Bcl10-Malt1 complex and leads to the induction of canonical and non-canonical NF- κ B subunits and IRF1, resulting in gene transcription (177, 178). Recently, CARD9 was found to be dispensable for NF- κ B activation, but regulated ERK activation by linking Ras-GRF1 to H-Ras (179). The CARD9 pathway is utilized by several other receptors (see also below) and is essential for protective antimicrobial immunity, particularly against fungi (180-182). Syk activation by Dectin-1 induces IRF5 and nuclear factor of activated T cells (NFAT), through PLC γ and Calcineurin (183, 184); a pathway inhibited by immunosuppressive drugs, such as cyclosporine, and linked to the increased susceptibility to fungal infection that occurs following administration of these compounds (185). The Syk-independent pathway from Dectin-1 involves activation of Raf-1, which integrates with the Syk-dependent pathway at the point of NF- κ B activation (186). Other pathways also exist. For example, the induction of phagocytosis by Dectin-1 in macrophages is Syk independent, requiring Bruton's tyrosine kinase (Btk) and Vav-1 (187, 188). The ability of Dectin-1 to induce productive intracellular signalling (ie: leading to cellular responses) requires receptor clustering into a "phagocytic synapse" and exclusion of regulatory tyrosine phosphatases (189). Moreover, the ability of Dectin-1 to induce

productive responses to purified agonists can be cell-type specific; an effect linked to differential utilization of CARD9 (190).

Activation of Dectin-1 signalling pathways can induce multiple cellular responses, including actin-mediated phagocytosis (Figure 3), phagosome maturation, activation of the respiratory burst, regulation of NET formation in neutrophils, DC maturation and antigen presentation, in part through the use of autophagy machinery (191-194). Dectin-1 can activate inflammasomes, facilitating the production of IL-1 β . Indeed, this receptor has been implicated in activation of the NLRP3 inflammasome, although the pathways involved are unclear, and can directly induce the non-canonical Caspase 8 inflammasome, through CARD9 and MALT1 (195-197). Assembly and activation of the Caspase-8 inflammasome was recently shown to require the non-receptor tyrosine kinase Tec (198). Dectin-1 also induces the production of eicosanoids, several cytokines and chemokines (including TNF, IL-10, IL-6, IL-23, CCL2, CCL3), and can modulate cytokine production and cellular functions induced by other PRRs. For example, costimulation of Dectin-1 and MyD88-coupled TLRs leads to the synergistic production of cytokines, such as TNF and IL-23, while simultaneously repressing the induction of others, such as IL-12 (199, 200). Another example is the ability of Dectin-1 to activate complement receptor 3 (CR3, alternatively Mac-1), through activation of Vav1, Vav3 and PLC γ , which results in enhanced neutrophil phagocytosis and ROS production (201). These two receptors also act collaboratively in macrophages, through association in lipid rafts and activation of the Syk-JNK-AP-1 pathway, to enhance inflammatory cytokine responses (202).

Like the TLRs, Dectin-1 is capable of instructing the development of adaptive immune responses, particularly Th1 and Th17 immunity (203). Interestingly, Dectin-

1-activated DCs can also instruct Treg (CD25⁺Foxp3⁺) to express IL-17 (204). While Th1 responses are important for the control of systemic infections, Th17 responses are critical for controlling fungal infections at the mucosa. Indeed, several human diseases associated with chronic mucocutaneous candidiasis, including CARD9 deficiency, have been linked to alterations in components of the Th17 response (205). How Dectin-1 promotes Th17 responses is incompletely understood, but involves Malt1-dependent activation of the NF- κ B subunit c-Rel, which is required for the induction of polarizing cytokines such as IL-1 β , and IL-23p19 (206). Dectin-1 can also induce humoral responses (207), stimulate cytotoxic T-cell responses (208), and induce myeloid-derived suppressor cells which can suppress T and NK cell responses (209). In addition to classic adaptive immunity, activation of Dectin-1 has been shown to induce innate immune memory (or trained immunity), through the epigenetic reprogramming of monocytes that occurs following aerobic glycolysis induced through an Akt-mTOR-HIF-1 α pathway (210, 211).

The role of Dectin-1 in driving adaptive immunity during infection is still not completely understood but there has been some recent progress. For example, Dectin-1 was found not to be essential for IL-17 production in mice systemically infected with *Candida albicans* (203), yet was required to drive Th17 polarization during pulmonary infection with *Aspergillus fumigatus* (162, 212). The ability of Dectin-1 to induce T helper cell differentiation during a skin infection model with *C. albicans* was recently shown to be dependent on fungal morphology (correlating with β -glucan exposure) and the dendritic cell subset involved (213). In the gastrointestinal tract (GI), Dectin-1 was found to be essential for driving fungal-specific CD4⁺ T-cell responses and for the maintenance of the cellularity of GI-associated lymphoid tissues (214). Dectin-1 can also regulate intestinal Treg cell

differentiation through modification of the microbiota, following exposure to dietary β -glucans (215).

MICL (CLEC-12A)

Myeloid Inhibitory C-type Lectin (MICL, also called DCAL-2, CLL-1, and KLRL-1) is structurally similar to Dectin-1, and located in the same genomic region (192). Unlike Dectin-1, MICL is one of the few myeloid expressed CLRs that contains an ITIM in its cytoplasmic tail and, like some of the Siglecs described above, can induce inhibitory intracellular signalling through SHP-1 and SHP-2 phosphates (216). Human MICL is alternatively spliced into at least three isoforms (α , β and γ), and the receptor is expressed as a monomer and heavily glycosylated (216). These latter features differ in the murine ortholog, which is expressed as a dimer and is only moderately glycosylated (217). In both species, MICL is expressed primarily by myeloid cell including macrophages, monocytes, dendritic cells and granulocytes, although the receptor is also expressed on B cells, CD8⁺ T-cells and bone-marrow NK cells in the mouse (217, 218). Expression levels of MICL are substantially regulated during inflammatory processes both *in vitro* and *in vivo* (217, 218). Interestingly, MICL is highly expressed on acute myeloid leukaemia (AML) cells, and the receptor has been put forward as a marker of this disease as well as for developing antibody-directed immunotherapies (219-222). In addition, murine MICL has been proposed to marker for a distinct subset of CD8 α^+ DC's (223). In mouse, targeting of antigens to MICL was found to induce CD4 and CD8 T-cell proliferation and enhance antibody responses (224).

MICL functions as an inhibitory receptor and experiments with receptor chimeras have directly demonstrated that MICL can inhibit the activation signals

induced through other PRRs (216). Moreover, antibody cross-linking experiments have shown that MICL can inhibit NK cell cytotoxicity (225) and differentially modulate DC responses, such as IL-12 production, depending on the mode of activation (226). Recently, MICL was shown to be regulated in an ATG16L1 (autophagy-related protein 16-like 1)-dependent manner, and play a key role in antibacterial autophagy through a functional interaction with an E3-ubiquitin ligase complex (227).

MICL recognises an endogenous ligand in many tissues and was recently identified as a receptor for dead cells and uric acid (217, 228). MICL was shown to be required to suppress the inflammatory responses induced by these ligands (228). Similar observations have been made with human leukocytes (229). Thus MICL appears to have an important role in controlling damage-induced inflammation and may be involved in autoimmune diseases. Indeed, MICL was recently found to play an essential role in regulating myeloid cell-mediated inflammation in a murine model of rheumatoid arthritis (RA) (230). Although polymorphisms of *CLEC12A* do not associate with RA, autoantibodies to MICL were identified in a subset of RA patients which, in mouse models, could exacerbate the disease (230). These findings suggest that the threshold of myeloid cell activation can be modulated by autoantibodies that bind to these types of inhibitory receptors. Downregulation of this receptor has also been proposed to underlie hyperinflammatory responses observed in Behçet's syndrome and gout (231).

Dectin-2 (CLEC4n)

Dectin-2 has a structure similar to that of Dectin-1, except that it possesses a short cytoplasmic tail lacking recognisable signalling motifs (232). To mediate

intracellular signalling, this receptor associates with the ITAM-containing FcR γ adaptor molecule (232). Dectin-2 is unusual in this respect in that its interaction with the adaptor is mediated by a membrane-proximal region within its intracellular tail, rather than through a transmembrane arginine residue as occurs with other similarly structured receptors (233). Like Dectin-1, signalling from the ITAM motif following Dectin-2 ligation occurs through the Syk, PKC δ and CARD9–BCL10–Malt1 pathway, but also involves Phospholipase C γ 2 (233-238). Dectin-2 is expressed primarily by myeloid cells, including macrophages, subsets of DC, neutrophils as well as monocytes, where its expression can markedly upregulated during inflammation, (206, 239-241).

Dectin-2 recognises high mannose based structures through its 'classical' carbohydrate-binding CTLD, which possesses a conserved EPN motif (242). This ligand specificity enables recognition of a variety of pathogens (including bacteria and nematodes for example) and pathogen-derived molecules (including house dust mite allergens) (232). Recently, Dectin-2 was shown to recognise mannose-capped lipoarabinomannan of mycobacteria, and play a role in anti-mycobacterial immunity (243). However, most attention has focussed on the role Dectin-2 in antifungal immunity, where it is required for protection against infection with selected fungal species, including *C. albicans* (through recognition of α -mannans on specific morphological forms) and *C. glabrata* (233-236, 244). Dectin-2 can also recognise species of *Malassezia*, through an O-linked mannanose-rich glycoprotein, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Fonsecaea pedrosoi* and *A. fumigatus* (245-249). In addition to pathogens, Dectin-2 may recognise an endogenous ligand and be involved in modulating UV-induced immunosuppression (250).

Like Dectin-1, Dectin-2 induces several cellular responses in response to microbial stimuli and can influence the development of adaptive immunity. In response to *C. albicans*, for example, Dectin-2 was shown to drive inflammatory host cytokine responses, including TNF, IL-6 and IL-12, and the development of T_h17 and T_h1 immunity (233, 235, 236, 248). Notably, Dectin-2 was found to selectively induce T_h17-polarizing cytokines including IL-23 and IL-1 β , by activating the NF- κ B subunit, c-Rel, via Malt1 (206). More recently, Dectin-2 was found to regulate a key neutrophil IL-17 autocrine loop during fungal infection (247). This receptor also plays a role in the physical recognition of fungi, and signalling from Dectin-2 can induce Nlrp3 inflammasome activation, extracellular trap formation, the respiratory burst, and production of cysteinyl leukotrienes (238, 241, 251-254). Dectin-2 may also form heterodimeric complexes with MCL (Dectin-3), although this is still controversial (255, 256).

The induction of cysteinyl leukotrienes, in particular, has led to a great deal of interest in the role of Dectin-2 in airway inflammation induced by house dust mite (HDM). This CLR can recognise a glycan component of HDM, inducing the production of cysteinyl leukotrienes by DC and stimulating the development of Th2 responses (252, 257). In mouse models of HDM-mediated pulmonary inflammation, Dectin-2 drove eosinophilic and neutrophilic responses by promoting both Th17 and Th2 immunity (257-260). Despite a clear role for Dectin-2 in allergy and host defence in mouse models, there is only one report demonstrating a link between polymorphism in this receptor and human disease (pulmonary Cryptococcosis) (261).

MINCLE / MCL (CLEC4D / CLEC4e)

Macrophage inducible C-type lectin receptor (Mincle) and Macrophage C-type lectin (MCL, also known as CLECSF8 or Dectin-3) are similar in structure to Dectin-2, but are discussed here together because they form a heterotrimeric complex (along with the ITAM-containing FcR γ adaptor) that is required for expression at the cell surface (256, 262-265). The FcR γ adaptor appears to associate primarily with Mincle, through a positively charged arginine residue in the transmembrane domain, and can induce signalling through the Syk, PKC δ , CARD9–Bcl10–Malt1 and MAPK pathways leading to activation of transcription factors, including NF- κ B (237, 262, 266). This adaptor can also associate with MCL, but this occurs in an unusual fashion independently of any charged amino acid residue in the transmembrane or cytoplasmic domain (264, 267). The association of MCL with Mincle is mediated by the stalk region, and expression of these receptors is co-ordinately regulated under naïve and inflammatory conditions (256, 265). The CTLD of MCL has also been shown to be involved in regulating surface expression (267).

Unsurprisingly, given that they function as complex, there is significant overlap in the reports describing the expression and function of Mincle and MCL. Both these receptors have been described as being predominantly expressed myeloid cells, including macrophages, neutrophils, monocytes and DC, although there is also evidence of expression on other leukocytes, including some subsets of B cells (256, 262, 267-273). Expression of these receptors can be upregulated following exposure to inflammatory stimuli, including microbial components such as LPS, and for Mincle this has been shown to occur in a MyD88 and C/EBP β -dependent manner (256, 274, 275). Mincle has also been reported to be reciprocally

expressed on neutrophils and monocytes within individuals, which has functional implications (269).

Mincle and MCL have both been shown to induce and / or regulate numerous cellular responses including endocytosis, phagocytosis, the respiratory burst, activation of the Nlrp3 inflammasome, neutrophil extracellular trap (NET) formation and the production of pro-inflammatory cytokines and chemokines (TNF, MIP-2, IL-1 β , MIP-1 α , IL-6, KC, G-CSF and MIP-2 for example) (237, 255, 262-264, 267, 272, 276-279). Moreover, both receptors can modulate the development of adaptive immunity, promoting Th1 and Th17 responses (264, 277, 278). Mincle has also been shown to promote Th2 development, by suppressing Dectin-1-mediated IL-12 production (178).

The CTLD of Mincle contains a classical mannose-recognition EPN motif but the receptor appears to primarily recognise microbial glycolipids (280-283). Specific microbial ligands have been identified, including mycobacterial cord factor, trehalose dimycolate (TDM), its synthetic analogue trehalose dibehenate (TDB), and glycerol monomycolate from mycobacteria, and glyceroglycolipid and mannitol-linked mannosyl fatty acids from fungi (245, 277, 284). Structural analysis suggests that Mincle's CTLD has binding sites for both the sugar and fatty acid moieties of these ligands (282, 283). In contrast, the CTLD of MCL is unable to directly recognise carbohydrates (267), but this receptor can recognise TDM (264). Structural analysis has suggested that, like Mincle, the CTLD may interact with both the sugar and fatty acid moieties of this glycolipid (282).

Given the ability of these CLRs to recognise mycobacterial components, it is not surprising that both receptors have been implicated in anti-mycobacterial immunity. In response to mycobacterial ligands, for example, Mincle induces the

production of inflammatory cytokines, nitric oxide, granuloma formation, and T_H1 and T_H17 responses (271, 272, 277, 278, 285). These activities of Mincle contribute to the adjuvant activities of complete Freund's adjuvant (286). MCL was similarly found to be required for the adjuvant activity of TDM, and loss of this receptor impaired both innate (inflammation, granuloma formation) and adaptive responses (T-cell function) induced by this glycolipid (264). Mincle has also been shown to recognise intact mycobacteria *in vitro*, but its actual role *in vivo* during infection is still unclear (277, 278, 287). One group has reported no effect of Mincle-deficiency on infections with *M. tuberculosis* H37Rv, whereas other groups have described some alterations in inflammation and bacterial burdens following infection with *Mycobacterium bovis* BCG or *M. tuberculosis* Erdman (271, 287, 288). In contrast, MCL was recently discovered to have an essential role in the non-opsonic recognition of mycobacteria by myeloid cells, and loss of this receptor resulted in higher extracellular mycobacterial burdens which drove neutrophilic inflammation and increased mortality in mouse models (289). Importantly, a polymorphism of MCL was also shown to be associated with susceptibility to tuberculosis in humans (289).

Both Mincle and MCL can also recognise other bacteria, including *Klebsiella pneumoniae*. During *K. pneumoniae* infection, for example, MCL^{-/-} mice showed increased susceptibility and presented with increased bacterial burdens, inflammatory neutrophilic responses, and severe lung pathology (290). Mincle has similarly been found to be required for the control of *K. pneumoniae* infection in mouse models (279).

Mincle was first characterised as receptor for *C. albicans* (291), and in response to this fungal pathogen, Mincle can induce protective immune responses including phagocytosis, fungal killing and inflammatory cytokine production (269,

291). As mentioned above, Mincle was found to be reciprocally expressed on leukocytes within the same individuals, and in monocytes expression correlated with reduced fungal uptake and killing, but enhanced inflammatory cytokine production. In contrast, expression of Mincle on neutrophils correlated with enhanced fungal uptake and killing (269). MCL^{-/-} mice were also shown to display increased susceptibility to *C. albicans*, with higher fungal burdens, and defective inflammatory responses (255). However, these observations are controversial, as other groups have not found any evidence for a role of MCL in anti-Candida immunity (263, 267, 289).

Mincle has been implicated in immunity to *Malassezia* and was found to be required for cytokine induction and inflammation during *in vivo* infection (280). In addition, Mincle recognises *Fonsecaea pedrosoi* and *F. monophora*, causative agents of chromoblastomycosis (178, 292). In contrast to other fungal pathogens, this recognition was found to be inefficient, due to a lack of TLR costimulation, and contributed to chronicity of the infection (292). Moreover, in response to *F. monophora*, Mincle can suppress Dectin-1-mediated IL-12 production, promoting Th2 responses (178). Similarly, Mincle was shown to suppress Th17 cell differentiation induced by Dectin-2 (248).

Mincle also recognises endogenous ligands. Spliceosome-associated protein (SAP)130, released from necrotic cells, was shown to be a ligand for Mincle, although recognition occurred through a different binding site on its CTLD (262).

Mincle recognition of SAP130, induces inflammatory cytokine production (MIP-2 and TNF, for example) and neutrophil accumulation (262). Recently, human Mincle was also shown to recognise cholesterol crystals (293). This recognition of endogenous ligands suggests a role for Mincle in homeostasis, although our understanding of this function is still poor. There is emerging evidence, however,

suggesting that Mincle may be involved in rheumatoid arthritis, pathogenesis of ischemic stroke and early brain injury after subarachnoid haemorrhage, and obesity-induced adipose tissue inflammation and fibrosis (294-298).

The Macrophage Mannose Receptor

The mannose receptor (MR, CD206) is a type I transmembrane protein that contains a heavily glycosylated extracellular region consisting of a cysteine rich domain, a fibronectin type II domain, and eight CTLDs (Figure 4) (299, 300). Two conformations of the MR have been proposed: an extended form and a more compact “bent” form that is influenced by pH (301). The MR is expressed predominantly intracellularly, as part of the endocytic pathway, in subsets of macrophages and DCs, as well as some other non-myeloid cell types including endothelial cells (300, 302). The expression of this receptor can be influenced by several cytokines, including IL-4 which causes marked upregulation of the MR (303). In fact, this upregulation has led to the MR being used as a marker for alternatively activated macrophages (304). Within the MR gene is a co-regulated microRNA (miR-511-3p), that modulates cellular activation in tumour associated and other macrophages and was recently shown to contribute to intestinal inflammation (305, 306). The extracellular domain of the MR can also be cleaved by metalloproteinases following cellular activation, through Dectin-1 signalling for example, releasing a functional soluble form (sMR) (307).

The extracellular domains of the MR each recognise different structures. The cysteine rich domain binds sulfated carbohydrates, the fibronectin domain binds collagen, while the CTLDs (specifically CTLDs 4-8) binds terminal mannose and fucose-based structures as well as N-acetyl glucosamine in a Ca²⁺-dependent

manner (300). The MR can also recognise CpG-motif containing oligodeoxynucleotides (308). The recognition of such a broad range of structures has led to substantial literature implicating the MR in both homeostasis and antimicrobial immunity. Indeed, the MR has been shown to recognise multiple types of pathogen, including viruses, helminths, trypanosomes, fungi and bacteria (166, 300).

Recognition by the MR has been proposed to induce several cellular responses, including endocytosis, phagocytosis, antigen cross-presentation and cytokine production, and modulate the development of adaptive immunity (300, 309, 310).

How the MR actually mediates many of these responses are unclear, as the receptor lacks known signalling motifs in its cytoplasmic tail, although its ability to mediate antigen cross presentation was shown to involve ubiquitination (311). In fact, its role in some of these responses is now controversial. For example, the MR was initially described as a phagocytic receptor, but subsequently shown not to be directly capable of mediating this activity (312, 313).

Several lines of evidence suggest that the effects ascribed to the MR may stem from collaboration with other receptors. For example, this receptor has been proposed to collaborate with Dectin-1 and the TLRs in the response to fungi such as *C. albicans* and *Paracoccidioides brasiliensis*, inducing the production of IL-17, Th17 and Tc17 cells (314-316). The differential responses to various MR ligands also support a notion for collaboration with other receptors from intracellular signalling. For example, mannan had no effect on DC cytokine production, yet other MR ligands, including mannose capped lipoarabinomannan (Man-LAM; a mycobacterial cell envelope molecule) and biglycan (an extracellular matrix proteoglycan), were found to influence cytokine responses in these cells (317). However, many of the ligands of the MR are recognised by other receptors, such as

Dectin-2 and Mincle (discussed above), and this overlapping specificity casts doubt on much of the early work.

Despite the considerable literature implicating the MR in immunity, studies of the MR-deficient mice have suggested that the functions of this receptor are largely redundant. These mice are viable and do not show significantly increased susceptibility to most infectious agents. For example, loss of the MR did not alter the susceptibility of mice to infection with *M. tuberculosis*, *C. albicans* or *P. carinii* (318-320). On the other hand, the MR-knockout mice were found to have slightly increased susceptibility to infections with *C. neoformans*, due to alterations in development of protective CD4 T cell responses (321). Deficiency of the MR has also been shown to lead to alterations in the regulation of serum glycoprotein homeostasis and the development of crescentic glomerulonephritis as well as allergic responses to cat allergens such as Fel D1, (322-324). In humans, polymorphisms in MR have been linked to susceptibility to asthma, sarcoidosis and tuberculosis (325-327)

Conclusion

Research over the last few decades has provided exciting new insights into the wide and varied functions of lectins. Through their ability to recognise carbohydrates and other ligands, we now appreciate that these molecules are an essential component of multicellular existence. As our understanding of the physiological roles of these receptors increases, opportunities for novel therapeutic approaches are emerging, such as the targeting of these receptors to drive vaccine responses (328). Yet, there is still much we need to learn. For example, we tend to study these molecules in isolation, but it is clear that these receptors function in a coordinated and cooperative

fashion. Indeed, the recognition of intact pathogens involves numerous receptors which trigger multiple intracellular signalling pathways, producing an integrated cellular response. Despite the importance of such receptor cross-talk we still understand very little about how such signalling is integrated and how this directs the final immunological response. We also know relatively little about the regulation and influence of glycosylation on homeostasis and immune function, or the recognition mechanisms that are involved. Tackling these important problems is a priority for future research.

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Figure Legends:

Figure 1: Siglecs in humans and mice. There are two subgroups of siglecs: One group contains siglecs that are conserved in all mammalian species and the other group contains CD33-related Siglecs which appear to be undergoing rapid evolution in primates. (ITIM) Immunoreceptor tyrosine-based inhibitory motif. The cell types expressing highest levels of each siglec are indicated. B, B cell; Eos, eosinophil; Mac, macrophage; mDC, myeloid dendritic cell; Mon, monocyte; Neu, neutrophil; NK, NK cell; Oli, oligodendrocyte; Ost, osteoclast; pDC, plasmacytoid dendritic cell; Pla, placental syncytiotrophoblast; Sch, Schwann cell

Figure 2: Selected signal transduction cascades induced by C-type lectin receptors. Activation receptors, such as Dectin-1, Dectin-2, Mincle and MCL, induce cellular responses primarily through Syk-kinase, although other pathways can be involved, such as those induced by Raf-1. Inhibitory receptors, such as MICL, activate protein tyrosine phosphatases (PTP: such as SHP-1) which attenuate activation pathways. DNGR-1 (CLEC9A), not discussed in the text, is an actin binding receptor expressed by CD8⁺ DC and involved in antigen cross-presentation. Reprinted with permission from (329).

Figure 3: Dectin-1 can mediate the non-opsonic phagocytosis of fluorescently labelled fungal particles (green) via actin (red)-based phagocytic cups. Reprinted with permission from (155).

Figure 4: The macrophage mannose receptor. Structure of the MR indicating its exogenous and endogenous ligands (including those in tissues). MØ, macrophage;

HBV, hepatitis B virus; CPS, capsular polysaccharide; SEA, secreted egg antigen; Adam-13, a disintegrin and metalloprotease 13. Reprinted with permission from (300).

Table 1: Lectin families

Family name	Selected Ligands
Calnexin	Glc ₁ Man ₉
Chitinase-like lectins	GlcN, GalN, chitin, Chito-oligosaccharides
C-type lectins	various (eg: Mannose, fucose, GalNAc, β -glucan)
F-box lectins	high mannose and sulfated glycoproteins
Ficolins	GlcNAc, GalNAc, fucose
F-type lectins	Fucose and others (eg: 3-O-methyl-D-galactose)
Galectins	β -Galactosides (eg: N-acetyllactosamine)
Intelectins	galactofuranose, pentoses
L-type lectins	various (eg: oligomannose)
M-type lectins	high mannose glycans (eg: Man ₈ GlcNAc ₂)
P-type lectins	mannose 6-phosphate
R-type lectins	various (eg: GalNAc, sialic acid, sulfated glycans)
Siglecs (I-type lectins)	sialic acid